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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,442	BRAUN ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,10-15 and 18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,10-15 and 18-29* is/are rejected.

7)☒ Claim(s) *18, 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 08-02-2007 has been entered.
3. Status of claims. Claims 1-4, 7-8, 10-15, 18-29 are currently pending. Claims 1, 3, 4, 7 and 8 have been amended, claims 5-6, 9, 16-17 have been canceled and claims 20-29 have been added by applicants amendment filed on 07-26-2007. The examiner acknowledges inadvertently leaving out of examination claims 17-19 of the preliminary amendment submitted on July 22, 2004 in the office action filed on 04-02-2007.
4. Therefore claims 1-4, 7-8, 10-15, 18-29 are currently being examined to which the following grounds of rejection are applicable.

5. ***Withdrawn objections/rejections in response to Applicant arguments or amendments.***

Nucleotides and/or amino acid sequences

In view of Applicants amendment to the claims and specification to include sequence identifiers to claims 3 and 8 and to the paragraph of the specification at page 4, paragraph 4 and at pages 5-6, in accordance with the requirements of *37* CFR 1.821 through 1.825, the objection to lack of compliance with amino acid sequence and/or nucleotide sequence requirement has been withdrawn.

Claim objection

In view of applicants' cancellation of claim 9, objection to claim 9 is moot.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of applicants' cancellation of claim 16, rejection of claim 16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is moot.

Claim Rejections - 35 USC § 101

In view of applicants' cancellation of claim 16, rejection of claim 16 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, is moot.

6. Rejections maintained in response to Applicant arguments or amendments.

35 USC § 112- First paragraph- Written description

Claims 1-4, 7-8, 10-15, 18-19 remain rejected and new claims 20-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Response to Applicants' arguments as they relate to rejection of claims 1-4, 7-8, 10-15, 18-19 remain rejected and new claims 20-29 are rejected under 35 U.S.C. 112, first paragraph.

On page 10 of Remarks, Applicants argue that transport peptides and their mechanisms of translocation were well recognized at the filing date of the application. Therefore, Applicants contend that "transport peptides which can penetrate the plasma membrane" are sufficiently described in their functional and structural characteristics, and as such the present claims are in compliance with the written description requirements. Moreover, Applicants cite the Pooga et al., (1998) and the Derossi et al., (1998) references, particularly at page 84, right column and at page 86, last paragraph to disclose support for transport peptides and their mechanisms of translocation that of skill in the art "would have immediately envisioned" with the kind of peptides encompassed by the claims. Such is not persuasive.

As stated in the previous office action, the instant claims encompass a genus of unidentified transmembrane peptides able of penetrating the plasma membrane (e.g, mitochondrial carrier protein, ammonia transporters, Bacteriorhodopsin-like proteins including rhodopsin, transmembrane cytochrome b-like proteins, calcium ATPase transporter, Voltage-

gated ion channel and others). The disclosure of the specification is not deemed to be descriptive of the complete structure of a representative number of species of transmembrane peptides able to penetrate the plasma membrane encompassed by the claims as one of skill in the art cannot envision without undue experimentation all transport modules having transport activity based on the teachings in the specification. In relation to the Derossi publication, cited by Applicants, the reference refers to a very specific amino acid sequence of the homeodomain of Antennapedia third helix domain (e.g., residues 43-58), a Drosophila transcription factor, also known as penetratin-1, which possesses translocation properties compared to that of the entire homeodomain (p. 84, col. 84). Even the recitation in new claim 20 of a transport peptide selected from "penetratin" could be broadly interpreted to encompass a genus of TPUs that are derived from the penetratin family and not necessarily to the Antennapedia third helix domain, as such there is no structure/function relationship taught at all for a transport peptide selected from "penetratin" as encompassed by new claim 20, let along for any transmembrane transport peptide. In addition, the Derossi publication at page 86, last paragraph, teaches widely divergent internalizing peptides in terms of their sequences, which leads the author to recite " it would be of interest to see how many internalizing sequences can be derived from these other molecules. We could them compare all internalizing sequences, model the peptides and search for conserved structural traits'. This statement clearly indicates that further search is necessary to establish the correlation of transport molecules and their functional and structural characteristics.

In so far as the language "address module", Applicants position on page 10 of remarks, is that, at the time of filing, it was well known that PNA oligomers hybridize to complementary

mRNAs, and the specification further discloses mRNAs which expression or mis-expression is associated with a tumor disease. As such, Applicants argue, the claims present sufficient disclosure of the functional phrase " hybridizes with a mRNA the expression or mis- expression is associated with a tumor disease" because respective target sequences of tumor genes were known in the art, therefore having the complementary sequence can be easily obtained by solid phase peptide synthesis as shown in Example 1 (c) of the specification. Such is not persuasive.

As stated in the previous office action, the "address module" which is a peptide nucleic acid (PNA) which hybridizes with a mRNA, the expression or miss-expression of which is associated with a tumor disease, is broadly interpreted as undefined number of nucleotide sequences which hybridize to a mRNA with the intended use of diagnosing a tumor disease. The specification teaches the nucleotide of SEQ ID No. 5 complementary to a region of Exon II of the c-myc mRNA and **the c-myc, c-ras, hern, sst1, sst2 mRNA** of genes associated with apoptosis and/or proliferation on human tumors, that were well known in the art . However, the specification is silent about regions or domains of the "address module" which is a peptide nuclei acid (PNA), which hybridizes with mRNA, essential for tumor disease, other than the PNA of SEQ ID No. 5 and peptide nucleic acid sequences able of hybridizing with c-myc, c-ras, hern, sst1 or sst2 mRNA . There is no structure/function relationship taught at all for a genus of claimed **address modules** other than the full length of nucleotide of SEQ ID No. 5 and PNA sequences able of hybridizing with c-myc, c-ras, hern, sst1 or sst2 mRNA. At page 13, Example 1, last paragraph, cited by Applicants in support of a genus of PNA sequences hybridizing with mRNAs associated with tumors, the specification merely teaches differentiation between tumor and non-tumor cells in lymphocytes by using product # 153a (i.e., **ACGT**) and product # 153b

(i.e., **RCGT**) containing c-myc-targeted peptide nucleic acids complementary to the c-myc mRNA in the cytoplasm and generated by solving stochiometric amounts of peptide-DTPA and the ion $Gd3^{+}$ (Sigma) resulting in the complexes $Gd3^{+}$-DTPH-lys-lys (linker)-Anti-Sense (PNA)-Cys –TPU constructs (p. 11, paragraph 1; table 1). Therefore, the specification does not describe a genus of **address modules** other than SEQ ID No. 5 and PNA sequences able of hybridizing with c-myc, c-ras, hern, sst1 or sst2 mRNA, in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these **address modules** at the time of filing the present application. Thus, the written description requirement has not been satisfied.

In relation to "the signaling module", Applicants argue on page 11 of Remarks that claim 1 has been amended to recite three modules the description of both structural and functional characteristics are sufficiently described..

As stated in the previous office action, only one example is disclosed for the signaling module, the $Gd3^{+}$-DTPH. There is no disclosure of any other contrast agents conjugated to the peptide-DTPA, nor disclosure of structure/function relationship taught at all for claimed signaling modules other than $Gd3^{+}$-DTPH.

Moreover, the examiner notices that claim 1 is drawn to species, Gadolinium (Gd), iron and fluoride that were originally restricted in the initial requirement for election/restriction in the office action filed on 12-13-2006. Applicants elected Gd in the response to the restriction requirements filed on 01-16-2007, therefore the claim 1 is examined to the extend that relates to the elected species.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

In view of the teaching of the art at the time the invention was filed identifying several cancer associated proteins as evidence by the Schiavone et al., publication, which represent potential targets for a selective peptide nucleic acid (PNA) as part of a tumor imagining diagnostic conjugate such as genes associated with apoptosis and/or proliferation (e.g., c-myc, c-ras, hern, sst1, sst2), the scope of enablement has been modified.

Claims 1-4, 7-8, 10-15, 18-19 remain rejected and new claims 20-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A diagnostic conjugate for the molecular imaging of a human tumor expressing a c-myc, c-ras, hern, sst1 or sst2 gene comprising in sequential order:

> a transmembrane transport peptide of SEQ ID Nos. 2, 3 or 4, conjugated via a cleavable linker to the a peptide nucleic acid which hybridizes with a c-myc, c-ras, hern, sst1 or sst2 mRNA, conjugated via a linker to a $Gd3^+$ complex, wherein said target specific antisense conjugated $Gd3^+$ transporter complex is transported across the cell membrane, wherein a hybrid is formed of said an antisense peptide nucleic acid and the RNA target sequence, wherein said hybrid begins to be slowly enzymatically cleaved, thereby releasing the target specific antisense conjugated $Gd3^+$ transporter,

does not reasonably provide enablement for a diagnostic conjugate as broadly claimed.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

Response to Applicants' arguments as they relate to rejection of claims 1-4, 7-8, 10-15, 18-19 remain rejected and new claims 20-29 are rejected under 35 U.S.C. 112, first paragraph-scope of enablement.

On page 11 of Remarks, Applicants argue that transport peptides, and domains and regions of these peptides, which are important for mechanisms of translocation, were well recognized at the filing date of the application. Therefore, Applicants contend that one of skill in the art would have been enable at the time of filing to make and use the cited conjugates comprising the recited components parts. In so far as the "transport peptides which can penetrate the plasma membrane", Applicants cite the Pooga et a la., (1998) and the Derossi et al., (1998) references, in particular, Applicants argue that these publications teach domains and regions as well as variants thereof important for translocating properties. Further, Applicants indicate that the amino acid sequences of these peptides can be obtained by solid phase peptide synthesis without undue burden. Such is not persuasive.

The scope of the patent protection sought by the Applicant as defined by the currently amended claim 1 and claims **2-4, 7-8, 10-15, 18-29,** fails to correlate with the scope of enabling disclosure set forth in the specification for the reasons of record and the following reasons. The instant claims encompass a genus of unidentified transmembrane peptides able of penetrating the plasma membrane (e.g, mitochondrial carrier protein, ammonia transporters, Bacteriorhodopsin-like proteins including rhodopsin, transmembrane cytochrome b-like proteins, calcium ATPase transporter, Voltage-gated ion channel and others). The disclosure of the specification is not deemed to be descriptive of the complete structure of a representative number of species of

transmembrane peptides able to penetrate the plasma membrane as one of skill in the art cannot envision without undue experimentation all transport modules having transport activity based on the teachings in the specification. In relation to the Derossi publication, cited by Applicants, the reference refers to a very specific amino acid sequence of the homeodomain of Antennapedia third helix domain(residues 43-58), a Drosophila transcription factor, also known as penetratin-1, which possesses translocation properties compared to that of the entire homeodomain (p. 84, col. 84). The structural limitation of said domain is not present in the instant claims. Even the recitation of a transport peptide selected from "penetratin" in newly added claim 20 is broadly interpreted to encompass a genus of TPUs that are derived from the penetratin family and not necessarily to the Antennapedia third helix. The specification does not teach regions or domains of the penetrating genus with translocating properties. In addition, the Derossi publication at page 86, last paragraph, teaches widely divergent internalizing peptides in terms of their sequences, which leads the author to recite " it would be of interest to see how many internalizing sequences can be derived from these other molecules. We could them compare all internalizing sequences, model the peptides and search for conserved structural traits'. Though the art of record discloses widely divergent internalizing sequences, the art does not provide sufficient guidance to make and use a variety TPUs as embraced and set forth by the invention in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art.

Regarding the peptide nucleic acid (PNA) sequences which hybridizes with a mRNA, the expression or miss-expression of which is associated with a tumor disease, Applicants argue that the art, at the time of filing, teaches a clear and known relationship between the mRNA target

sequence of the claimed PNA which was understood and predictable, because a number of antisense studies were reported prior to the filing date and genes, expression of which was associated with at tumor disease, and their sequences readily available from the art as evidence by Shiavone et al., at pages 779 and 780. Further, Applicants contend that "contrary to antisense therapy it is not necessary that the PNA switch-off or modify expression of the target gene". Moreover, Applicants quote from Schiavone et al., "a wide number of oncogenes have been then successfully targeted with antisense oligos either in vitro or in vivo" (page 779, 1st column, 4th paragraph at the bottom) and as such a skilled person could have selected from those antisense sequences to make a PNA according to the invention without any undue burden. Such is not persuasive.

Though identification of several cancer associated proteins have been disclosed at the time of filing as evidence by the Schiavone et al., publication, which can represent potential targets for a selective tumor imagining diagnostic conjugate such as genes associated with apoptosis and/or proliferation (e.g., c-myc, c-ras, hern, sst1 or sst2 mRNA), identification of a genus of PNA sequences which hybridizes with a mRNA associated with a tumor disease has to be determine on a case-by case basis, as there is substantial variability among mRNAs associated with a tumor disease. In other words, a PNA which hybridizes to an Exon II of the c-myc mRNA or a PNA sequence able of hybridizing with a c-myc, c-ras, hern, sst1 or sst2 mRNA, which are genes well known in the art for their association with human tumors, wont be able to detect any mRNA associated with a tumor disease, as each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested and undue experimentation would be required to practice the invention as it is claimed in its current scope.

In relation to "the signaling module", Applicants argue on page 13 of Remarks that claim 1 has been amended to recite three modules, Gadolinium, iron and fluorine, which were well known to be used in tumor imaging at the time the application was filed, as such a skilled person could have made the claimed conjugates without undue experimentation or burden. Such is not persuasive

As stated in the previous office action and in the paragraph above, only one example is disclosed in the specification for the signaling module, the $Gd3^{+}$-DTPH. There is no disclosure of any other contrast agents conjugated to the peptide-DTPA, nor disclosure of structure/function relationship taught at all for claimed signaling modules other than $Gd3^{+}$-DTPH. Moreover, the examiner notices that claim 1 is drawn to species that were originally restricted the initial requirement for election/restriction in the office action filed on 12-13-2006. Therefore the claim 1 is examined to the extend that relates to the elected species.

Therefore, it would require undue experimentation to make and use other TPU able of penetrating the plasma membrane other than peptides of SEQ ID Nos. 2, 3 and 4 to be coupled to the AS via a covalently cleave spacer I, and other PNA address modules hybridizing to a mRNA, associated with a tumor disease, other than that of the a peptide nucleic acid which hybridizes with a c-myc, c-ras, hern, sst1 or sst2 mRNA, associated with a tumor disease, to generate an antisense-sequence-conjugated-Gadolinium-transporter; it certainty would require undue experimentation to make their corresponding DNA and, therefore, claims encompassing a genus of nucleic acids that may encode a TPU, AS and a SM other than the conjugated-Gadolinium-transporter are not enabled by the claimed embodiment.

Claim Rejections - 35 USC § 102

Claims 1, 2, 4, 7, 10, 12, 15, 18-19 remain rejected under 35 U.S.C. 102(e) as being anticipated by Collins et al, US Patent Application Publication 2006/0074034, Date of Publication April 6, 2007)

Response to Applicants' arguments as they relate to rejection of claims 1, 2, 4, 10, 12, 15, 18-19 under 35 USC § 102.

On page 14 of Applicants remarks, Applicants argue that claim 1, as amended, claims a transport peptide capable of penetrating the plasma membrane. Moreover, Applicants contend that Collin et al., teaches a compound comprising vitamin BI2 as carrier which is not the peptide of the transport encompassed by claim 1, as the vitamin BI2 compound is internalized by receptor mediated endocytosis. Further, Applicants argue that vitamin B12 cannot be considered a compound, which penetrates the plasma membrane. As such Collin et al., do not anticipate the instant claimed invention. Such is not persuasive.

Though Collin et al., teach as preferred embodiments vitamin BI2-mediated delivery of PNA, Collin et al., also disclose in alternated embodiments peptide sequences that have been shown to be able to carry PNA oligomers across the cell membranes including the rat transferrin receptor, peptide of the nuclear-encoded human cytochrome c oxidase (COX) subunit VIII, **penetratin, chimeric peptide transportan**, biotinyl-FLFL, a D-peptide analog of insulin-like growth factor 1 and others (page 3, paragraphs [0026-0028]) which are useful in the imaging of tumors [page 5, paragraph 0047]. Moreover, Collin et al., teach that exemplary oncogenes include but are not limited to neu, src, abl, lck, fyn, phl-abl, **H-ras, N-ras, K-ras, myc** and mos

(p.23, paragraph [0240]) and contemplate the development of that anti cancer antisense inhibitors (p.26, paragraph [0276]; p.27, paragraph [0278]).

It is noted that case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. In re Donohue, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. Bristol-Myers, 246 F.3d at 1379; see also In re Donohue, 766 F.2d at 533.

Claim Rejections - 35 USC § 103

Claim 1-7, 9, 15, 16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braun et al., (US patent No. 6,821,948), in view Cavaran et al.,. Bioconjug Chem. 1999 :361-70).

Response to Applicants' arguments as they relate to rejection of claims 1-4, 7, 15, 18-19 under 35 USC § 103.

At page 16 of Remarks, Applicants argue that Braun et al. do not describe use of a PNA as **an address module** as recited in claim 1". Additionally, Applicants contend, "Braun et al. provide peptides which can penetrate an intracellular membrane system or bind thereto (see col. 3, lines 33-52). However, it was known that such a PNA cannot penetrate or support penetration of a membrane system and, therefore, Braun et al. teach away from the use of such a PNA as an address module such as that recited in the claim 1". Moreover, in relation to Example 4, Applicants argue that "Braun et al. exemplify a conjugate made of a penetratin, a nucleus

localization sequence (NLS), and a PNA antisense to rats P2 promoter c-myc, i.e. a promoter sequence which is not transcribed into mRNA. Hence, Braun et al. teach a PNA antisense to c-myc DNA. Braun et al. do not describe a PNA which hybridizes with a mRNA of c-myc, as alleged by the examiner" . Such is not persuasive.

Amended claim 1 recites the limitation "a peptide nucleic acid which hybridizes with a mRNA, the expression or miss-expression of which is associated with a tumor". Though the anti sense PNA with respect to rats P2 promoter c-myc taught by Braun et al. at col. 8 in Example 4, does not hybridize to a mRNA as the promoter sequence clearly signal the start for RNA synthesis, other disclosed embodiments of "**an active substance**" in the '948 patent include **antisense RNA, antisense oligonucleotides** and **PNA** (col. 4, line 16-19) which can be targeted to transcribed DNA sequences other than non-transcribed DNA sequences of promoter regions. Thus **the active substance** taught by Braun et al. is the same as **the address module** encompassed by claim 1 because both components of the conjugate are PNA able to hybridize with mRNA, the expression or miss-expression of which is associated with a tumor disease. Therefore, it is unclear how Braun et al. teach away from the use of such a PNA **as an address module as claimed.**

At page 16 of Remarks, Applicants have requested clarification about the examiner statement in relation **to the address proteins** taught by Braun et al. including SEQ ID No. 8, which presents a 100% homology to SEQ ID No. 3 of the instant invention .

The examiner inadvertently indicated in the previous office action that that SEQ ID No. 8 and not SEQ ID No. 13 was identical to SEQ ID NO: 3 of the instant invention. A new copy of

the alignment of SEQ ID NO: 13 of the '948 patent and SEQ ID No. 3 of the instant invention is submitted hereof (See, SCORE Search Results for Application 10/502442- SEQ ID Nos. 3, Resut 1)

In relation to the Braun's reference Applicants conclude that "Braun et al., does not provide any logical basis for claiming a PNA as an address module, as is recited in the claimed invention. **On the contrary, Braun et al. teach that a NLS as an address peptide is additionally necessary**. Therefore, Braun et al. do not provide any basis for I) attaching the PNA directly to the transport peptide, 2) a PNA which hybridizes with a mRNA of a gene which expression or mis-expression is associated with a tumor diseases, or 3) labeling the peptide-PNA conjugate with Gadolinium" . Such is not persuasive.

I). Claim 1 as written encompasses any address module, which is able to penetrate the membrane. As such the conjugate taught by Braun et al. comprising a transport mediator and a cell-specific, compartment-specific or membrane-specific address protein/peptide (e.g., NLS) read on the instant claim (see Braun et al., claim 1); II) Braun et al. disclose "**an active substance**" including **antisense RNA, antisense oligonucleotides** and **PNA. As the** Braun et al. teaches PNA and antisense molecules, then any activity resulting form the expression or miss-exppression of the mRNA is implicitly anticipated because the structure of that PNA or antisense hybridizing to a complementary mRNA according to the Watson-Crick base paring rules in the same. Please, note "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997), and III) Additionally, Braun et

al. teaches that "the active substance may optionally be labeled, e.g. radioactively, with a dye, with biotin/avidin, etc" (col. 4, lines 10-13). Caravan et al., complements the teaching of Braun et al. by disclosing that it is routine or well established in the art to employ gadolinium as a contrast agent with other antibodies or tissue specific molecules to provide disease specific MRI agents. Thus the combination of the US patent No. 6,821,948 and the Cavaran et al., publication renders obvious the instant claimed invention with respect to a diagnostic conjugate comprising a TPU able of penetrating the plasma membrane, a AS which is a a PNA which hybridizes with a mRNA, and a SM consisting of Gadolinium.

New Grounds of Rejection

Claim objection

Claim 18 is objected because they depend from canceled claim 9. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 21 is vague and indefinite in that the metes and bounds of the phrase "the transport peptide is a human transport peptide" are unclear. Claim 21 depends from claim 20, which

recites as a TPU selected from the group consisting of penetratin and transportan. The transport protein "penetratin" is from the Antennapedia homeodomain from Drosophila melanogaster (see Derossi et al., p. 84, col. 2). Therefore, claims 21 by claiming a human transport peptide fails to further limit claim 20. Likewise, transportan is a 27 amino acid chemically synthesized which comprises the aminus terminal form the neuropeptide galanin and the carboxyl terminal form mastoparan, a 14-amino acido long-wasp venom peptide toxin (see Pooga et al., 1998, p. 67, col. 1). It is unclear how the transport peptide of claim 21 depending on the transport peptides penetratin and transportan, which are not human, is human.

Conclusion

Claims 1-4, 7-8, 10-15, 18-29 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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